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OPPORTUNISTIC INFECTIONS AND KAPOSI'S SARCOMA IN HOMOSEXUAL MEN

IN the summer of 1981, the Centers for Disease Control (CDC) alerted the medical world to an unexpected outbreak of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma in young homosexual men who had no known reason to contract these uncommon diseases.^{1,2} New and surprising though this association may be, enough cases have already been collected to establish its reality. More than 160 examples are now being analyzed at the CDC, and five or six new cases are being reported each week. Recently, eight cases of Kaposi's sarcoma in young homosexual men in New York City were reported in *Lancet*.³ In this issue, the *Journal* presents for our evaluation further detailed reports of the syndrome of opportunistic infections and Kaposi's sarcoma in homosexual men (three papers, 19 patients, and 32 authors).⁴⁻⁶

These salient features have emerged: The patients are typically young homosexual men, most of whom live in large cities and many of whom use drugs; the infectious agents are low-grade pathogens that often cause opportunistic infections in compromised hosts; and the death rate is fearfully high. Two thirds of the patients described in this issue of the *Journal* have died, as have more than one third of the patients on record at the CDC.

This development poses a puzzle that must be solved. Its solution is likely to be interesting and important to many people. Scientists (and the merely curious) will ask, Why this group? Why now, and not before? What does this tell us about immunity and the genesis of tumors? Students of public-health issues will want to put this outbreak into a social perspective. Gay associations, which are often active and well informed on pertinent health issues, will want to take measures to educate and protect their members. Humanitarians will simply want to prevent unnecessary death and suffering.

So far, at least a dozen microbial species have been shown to cause disease in these patients: among viruses, cytomegalovirus and herpes simplex virus; among bacteria, *Mycobacterium tuberculosis*, *M. avium-intracellulare*, *Klebsiella pneumoniae*, and other gram-negative aerobic bacilli; among fungi, *Candida albicans* and *Cryptococcus neoformans*; and among protozoa, *Pneumocystis carinii*, *Toxoplasma gondii*, and *Entamoeba histolytica*.

A glance at this list will establish two facts: The gap in host defenses is broad, not limited to those against any one class of microbe, and the pathogens are mostly those to be expected in patients with defective cellular immunity. This clinical evidence of a cellular defect is supported by the demonstration of cutaneous anergy, striking lymphopenia, T-lymphocyte depletion, decreased lymphocyte proliferative responses, and defective natural-killer-cell activity in these patients.⁴⁻⁶ Humoral immune responses seem to be normal.

The nature and multiplicity of these pathogens and the overwhelming severity of many of the illnesses indicate that the normal defenses are severely compromised. The clinical implication is that homosexuals with syndromes suggesting unusual infections should be investigated promptly and aggressively, like other immunocompromised patients. The physician should anticipate simultaneous multiple infections, poor response to treatment, and a tendency to relapse. Because the mortality is so high, invasive diagnostic procedures such as open-lung biopsy are fully justified. Until the cause of the apparent defect in host defenses is understood, the only available means to reduce mortality is early, specific therapy for each treatable infection. Long-term prophylaxis for pneumocystis pneumonia with trimethoprim plus sulfamethoxazole (as commonly used in children after treatment for lymphocytic leukemia) may be appropriate for patients with this syndrome,⁴ whether or not they have already had pneumocystis pneumonia.

The question of cause is obviously central. What clue does the link with homosexuality provide? Homosexual men, especially those who have many partners, are more likely than the general population to contract sexually transmitted diseases.⁷ Lesbians are not, and this apparent freedom, whatever its explanation, seems to extend to Kaposi's sarcoma and opportunistic infections. At present, only one woman is included among the patients known to the CDC. Male homosexuals are at increased risk for the acquisition of common viral infections, including those caused by hepatitis B virus, cytomegalovirus, and Epstein-Barr virus, and viruses can cause immunosuppression.^{8,9} Notably, many of the patients described by Gottlieb,⁴ Masur,⁵ and Siegal⁶ and their colleagues had an insidious, nonspecific illness marked by malaise, fever, weight loss, lymphadenopathy, and thrush for several months before the onset of more severe opportunistic infections. Were these features manifestations of a primary immunosuppressive viral disease? If so, both neoplasia and infection could be secondary phenomena, with Kaposi's sarcoma acting as an "opportunistic tumor" and the opportunistic infections representing a mode of death rather than the cause of death.

Evidence of previous or current cytomegalovirus infection is a common thread that runs throughout these case reports.¹⁻⁶ Cytomegalovirus causes immunosuppression in mice and human beings,^{8,9} and this virus can persist in semen for months at a high titer.¹⁰ The pattern of lymphocyte disturbances in these patients is similar to the changes found in patients with cytomegalovirus mononucleosis, which persist for months after recovery.⁹ Concurrent cytomegalovirus infection greatly increases the mortality of experimental bacterial and fungal infections in mice.⁸ In renal-transplant recipients, Rubin et al.¹¹ have shown that cytomegalovirus may be associated with leukopenia and may predispose the patient to other opportunistic in-

fections. Accordingly, Gottlieb and his colleagues⁴ can argue cogently that cytomegalovirus itself is highly suspect as the cause of this syndrome. On the other hand, more than 90 per cent of homosexual men in the community have antibodies indicating previous cytomegalovirus infection.¹² Therefore, positive cultures for cytomegalovirus could represent nothing more than reactivation of latent infection during immunosuppression, as happens predictably in transplant recipients.¹¹

What do young Africans, elderly Americans, renal-transplant recipients, and homosexual men have in common? The answer is Kaposi's sarcoma, a tumor that is found in these diverse groups for reasons that we do not yet understand.^{13,14} A search for the origins of this unusual neoplasm brings us back to cytomegalovirus, which has been implicated as a possible etiologic factor on the basis of serologic studies.¹³ Furthermore, the cytomegalovirus genome has recently been detected in Kaposi's-sarcoma tissue.¹⁵ The final answer on whether cytomegalovirus is a cause or an effect in this setting will carry important implications for tumor biology.

The cytomegalovirus hypothesis suffers from an obvious problem: It does not explain why this syndrome is apparently new. Homosexuality is at least as old as history, and cytomegalovirus is presumably not a new pathogen. Were the homosexual contemporaries of Plato, Michelangelo, and Oscar Wilde subject to the risk of dying from opportunistic infections? Certainly, a few cases caused by unusual microbes would have passed unnoticed among the welter of other deaths caused by common infections before the advent of modern microbiology, but what of recent times? Pneumocystis has been known for almost 30 years, and, given the right specimens and correct stains, it is fairly easy to identify. Present indications are that we are seeing a truly new syndrome, not explainable simply by failure to diagnose earlier cases. Therefore, we must suspect that some new factor may have distorted the host-parasite relation. So-called "recreational" drugs are one possibility. They are widely used in the large cities where most of these cases have occurred, and the only patients in the series reported in this issue who were not homosexual were drug users. Fashions in drug use change frequently, and experimentation with new agents is common. Perhaps one or more of these recreational drugs is an immunosuppressive agent. The leading candidates are the nitrites, which are now commonly inhaled to intensify orgasm. Users of amyl nitrite are more likely than nonusers to have had hundreds of sexual partners and to contract venereal diseases.¹⁶ Preliminary data indicate that this "liberated" subgroup may be at highest risk for immunosuppression.

In our present state of ignorance, some frank speculation seems permissible. Let us postulate that the combined effects of persistent viral infection plus an adjuvant drug cause immunosuppression in some genetically predisposed men. During the early stages,

patients may have only a nonspecific illness and minor infections such as thrush. Then Kaposi's sarcoma may develop as an opportunistic tumor (perhaps cytomegalovirus-induced), which is set free by a failure of immune surveillance. Finally, as the defect in cellular immunity becomes progressively more severe, serious opportunistic infections develop. According to this hypothesis, several factors may interact to form a final common pathway of immunosuppression, which then leads to both neoplasia and infection.

The authors of today's three reports deserve congratulations for making a prompt beginning to this investigation. But it is only a beginning. Enumeration of lymphocyte subpopulations, though certainly a fashionable pursuit, seldom seems to provide the final answers; other approaches will be necessary. The CDC, acting with customary dispatch, has commissioned a task force to unravel the tangled threads. Case-control studies to single out possible risk factors, such as promiscuous life styles and nitrite inhalation, are under way. Patients are being HLA-typed (when their lymphocyte counts are not too low for this test) in a search for a possible genetic predisposition. Examination or reexamination of the immunosuppressive potential of recreational drugs has begun. Some of the lymphocyte laboratories have been appropriately stimulated to look for mechanisms. These studies should answer the tantalizing questions raised by this new syndrome, perhaps providing means to protect the persons most at risk, and certainly extending our understanding of host-parasite relations.

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THE TOSS-UP

CONSIDERABLE turmoil is often created when expert physicians have different and strongly held opinions about the optimal treatment strategy for a given patient. Indeed, opinions may be widely discrepant: one clinician may recommend a risky surgical procedure, and the other may favor medical therapy; one may propose an invasive diagnostic test, and the other may dismiss the test as unnecessary and insist that the patient be treated without delay. Paradoxically, sometimes a surgeon advocates medical therapy while the internist recommends surgery. How do we explain these striking contrasts? Are some physicians naturally attracted to more aggressive treatments? Do some require more diagnostic certainty before beginning therapy? Are individual persons merely interpreting the same data in a different fashion, or are there important philosophical differences in approach? Can these differences be attributed, as previously suggested, only to variations in the physician, the patient, and the examination?^{1,2}

Perhaps all these factors are involved in clinical controversies, but we propose that one explanation has not been sufficiently recognized: that it simply makes no difference which choice is made. We suggest that some dramatic controversies represent "toss-ups" — clinical situations in which the consequences of divergent choices are, on the average, virtually identical. The hypothesis that some controversies represent toss-ups is based on our experience with clinical problems that are sufficiently difficult to warrant a request to our Division of Clinical Decision Making for consultation. These consultations are carried out by applying formal decision-analytic methods. Using decision analysis, we can quantify the value (or expected utility) of competing options, and assess whether the difference in utility between the options is clinically important. In applying decision analysis to more than 100 problems that expert physicians considered conundrums, we found that in one sixth of the cases the difference in expected utility between available choices was so small that we could not conceive of it as clinically relevant. Thus, many decisions that were perceived intuitively to be tough were shown on quantitative analysis to be toss-ups.